

Newborn Screening in Michigan

2004 Annual Report



*Michigan Department
of Community Health*



Jennifer M. Granholm, Governor
Janet Olszewski, Director

March 2005

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Prepared by the Michigan Department of Community Health

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Executive Summary

This inaugural report presents an overview of the Newborn Screening Program at the Michigan Department of Community Health (MDCH). The program includes three components: screening, follow-up and medical management. Statewide surveillance data from the Newborn Screening Program are also included for the year 2004, the first complete year of screening using tandem mass spectrometry.

The Newborn Screening Program began in 1965, when the state began screening infants for phenylketonuria. Ten additional disorders have been added to the screening panel since that time, and over five million infants have been screened through the statewide program. This report reviews the history of screening in Michigan, the legislative mandate for screening, and the current programmatic structure.

This report also describes the laboratory testing for each of the eleven disorders currently screened for in Michigan, with a section including detailed descriptions of each disorder. Data are presented on the quality assurance functions of the newborn screening program, and on the epidemiology of each of the disorders in 2004.

Family activities, supported by the Newborn Screening Program with guidance from the parent consultant, are described. Special projects supported by newborn screening staff are also presented, such as lectures at national conferences, special data linking projects, and a technical assistance review from national experts.

State and national resources are provided, such as the free, online tutorial for hospital and birthing staff about the newborn screening program, including proper collection of blood from infants. Condition-specific information and general resource information is included for healthcare providers and families.

Introduction

History of Newborn Screening in Michigan

The State of Michigan introduced newborn screening in 1965 when laboratory technology first became available to identify newborns with phenylketonuria (PKU). In 1977, a test for congenital hypothyroidism (CH) was added to the newborn screening panel, and in 1984, screening for galactosemia was initiated. Public Act 14 of 1987 mandated further expansion of screening, with the addition of three disorders: biotinidase deficiency, maple syrup urine disease (MSUD), and hemoglobinopathies such as sickle cell disease. The act also designated the state laboratory as the sole testing site, mandated a fee to fund the program, and added comprehensive programs for follow-up, medical management, and quality assurance. Congenital adrenal hyperplasia was added to the panel in 1993. The introduction of tandem mass spectrometry in 2003 enabled the state laboratory to begin screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD) in 2003 and homocystinuria, citrullinemia and argininosuccinic aciduria (ASA) in 2004.

Conditions Screened for in Michigan by Year of Initiation

1965	Phenylketonuria (PKU)
1977	Congenital Hypothyroidism (CH)
1984	Galactosemia
1987	Biotinidase Deficiency Hemoglobinopathies Maple Syrup Urine Disease (MSUD)
1993	Congenital Adrenal Hyperplasia (CAH)
2003	Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (MCADD)
2004	Argininosuccinic Aciduria (ASA) Citrullinemia Homocystinuria

Enabling Legislation

The newborn screening program is legislatively mandated through Public Health Code Act 368 of 1978 with additional amendments from 1986 through 2003. The specific enabling legislation is written as follows:

333.5431 Testing newborn infant for certain conditions; reporting positive test results to parents, guardian, or person *in loco parentis*; compliance; fee; “Detroit consumer price index” defined; violation as misdemeanor; hardship waiver; conduct of department regarding blood specimens; pamphlet; additional blood specimen for future identification.

Sec. 5431.

- (1) A health professional in charge of the care of a newborn infant or, if none, the health professional in charge at the birth of an infant shall administer or cause to be administered to the infant a test for each of the following:
 - (a) Phenylketonuria.
 - (b) Galactosemia.
 - (c) Hypothyroidism.
 - (d) Maple syrup urine disease.
 - (e) Biotinidase deficiency.
 - (f) Sickle cell anemia.
 - (g) Congenital adrenal hyperplasia.
 - (h) Medium-chain acyl-CoA dehydrogenase deficiency.
 - (i) Other treatable but otherwise disabling conditions as designated by the department.
- (2) The informed consent requirements of sections 17020 and 17520 do not apply to the tests required under subsection (1). The tests required under subsection (1) shall be administered and reported within a time and under conditions prescribed by the department. The department may require that the tests be performed by the department.
- (3) If the results of a test administered under subsection (1) are positive, the results shall be reported to the infant's parents, guardian, or person *in loco parentis*. A person is in compliance with this subsection if the person makes a good faith effort to report the positive test results to the infant's parents, guardian, or person *in loco parentis*.
- (4) Subject to the annual adjustment required under this subsection and subject to subsection (6), if the department performs one or more of the tests required under subsection (1), the department may charge a fee for the tests of not more than \$53.71. The department shall adjust the amount prescribed by this subsection annually by an amount determined by the state treasurer to reflect the cumulative annual percentage change in the Detroit consumer price index. As used in this subsection, "Detroit consumer price index" means the most comprehensive index of consumer prices available for the Detroit area from the bureau of labor statistics of the United States department of labor.
- (5) A person who violates this section or a rule promulgated under this part is guilty of a misdemeanor.
- (6) The department shall provide for a hardship waiver of the fee authorized under subsection (4) under circumstances found appropriate by the department.

- (7) The department shall do all of the following in regard to the blood specimens taken for purposes of conducting the tests required under subsection (1):
- (a) By April 1, 2000, develop a schedule for the retention and disposal of the blood specimens used for the tests after the tests are completed. The schedule shall meet at least all of the following requirements:
 - (i) Be consistent with nationally recognized standards for laboratory accreditation and federal law.
 - (ii) Require that the disposal be conducted in compliance with section 13811.
 - (iii) Require that the disposal be conducted in the presence of a witness. For purposes of this subparagraph, the witness may be an individual involved in the disposal or any other individual.
 - (iv) Require that a written record of the disposal be made and kept, and that the witness required under subparagraph (iii) signs the record.
 - (b) Allow the blood specimens to be used for medical research during the retention period established under subdivision (a), as long as the medical research is conducted in a manner that preserves the confidentiality of the test subjects and is consistent to protect human subjects from research risks under subpart A of part 46 of subchapter A of title 45 of the code of federal regulations.
- (8) The department shall rewrite its pamphlet explaining the requirements of this section when the supply of pamphlets in existence on March 15, 2000 is exhausted. When the department rewrites the explanatory pamphlet, it shall include at least all of the following information in the pamphlet:
- (a) The nature and purpose of the testing program required under this section, including, but not limited to, a brief description of each condition or disorder listed in subsection (1).
 - (b) The purpose and value of the infant's parent, guardian, or person *in loco parentis* retaining a blood specimen obtained under subsection (9) in a safe place.
 - (c) The department's schedule for retaining and disposing of blood specimens developed under subsection (7)(a).
 - (d) That the blood specimens taken for purposes of conducting the tests required under subsection (1) may be used for medical research pursuant to subsection (7)(b).
- (9) In addition to the requirements of subsection (1), the health professional described in subsection (1) or the hospital or other facility in which the birth of an infant takes place, or both, may offer to draw an additional blood specimen from the infant. If such an offer is made, it shall be made to the infant's parent, guardian, or person *in loco parentis* at the

time the blood specimens are drawn for purposes of subsection (1). If the infant's parent, guardian, or person *in loco parentis* accepts the offer of an additional blood specimen, the blood specimen shall be preserved in a manner that does not require special storage conditions or techniques, including, but not limited to, lamination. The health professional or hospital or other facility employee making the offer shall explain to the parent, guardian, or person *in loco parentis* at the time the offer is made that the additional blood specimen can be used for future identification purposes and should be kept in a safe place. The health professional or hospital or other facility making the offer may charge a fee that is not more than the actual cost of obtaining and preserving the additional blood specimen.

Funding

The Newborn Screening Program is funded through fees generated from the purchase of the initial blue screening card. Hospitals and birthing attendants purchase the cards to have available to complete after a birth. The revenue collected from sale of the cards allows the state to offer laboratory, follow-up, and medical management services to all Michigan families. If a newborn requires a repeat newborn screening sample, a pink card is used. Pink cards are provided at no additional charge.

Newborn Screening - Michigan Department of Community Health
Bureau of Laboratories P.O. Box 30689 3150 N. MLK Jr. Blvd. Lansing, MI 48909
DCH 1153 L-XXXXXX Print Family with Pen

BABY
LAST NAME FIRST NAME GENDER
BIRTH DATE BIRTH TIME (Military) BIRTH TIME (Civil) VAGINOECTOMY
COLLECTED TIME (Military) COLLECTED TIME (Civil) NICU SPECIAL CARE? RBC TRANSFUSION?
MEDICAL RECORD # DATE
TPN FEEDING? YES NO
HERPANGIA NON-HERPANGIA WHITE AMERICAN INDIAN MIDDLE EASTERN
BLACK ASIAN/PACIFIC ISLAND MULTIRACIAL

MOTHER
LAST NAME FIRST NAME
ADDRESS PHONE
CITY STATE ZIP SOCIAL SECURITY NUMBER
MEDICAL RECORD # BIRTH DATE TEST DATE HEPATITIS B SURFACE ANTIGEN (HBsAg)
TEST RESULT POSITIVE NEGATIVE

SUBMITTER
SUBMITTER NAME FIRST NAME LAST NAME
ADDRESS PHONE
CITY STATE ZIP
BIRTH HOSPITAL (Date of institution admission)

1234567
HOSPITAL CODE (if applicable)
MDCH USE ONLY

Figure 1. Image of initial blue newborn screening card.

Overview of the Michigan Newborn Screening Program

Hospitals

As specified in the Public Act 14 of 1987, as amended by Act 264 of 1988, the health care provider in charge of the care of an infant at birth is responsible for assuring that a newborn screen is performed. Since most Michigan infants are born in hospitals, nursery and/or laboratory staff assume primary responsibility for obtaining a specimen from every infant delivered at the institution. This responsibility includes ordering newborn screening cards, completing the newborn screening card in an accurate and legible manner, obtaining a satisfactory blood spot specimen, and sending the card and the blood spots in a timely manner to the state newborn screening laboratory.

Midwives and Home Birth Attendants

The nurse midwife or other attending health professional is responsible for submitting specimens for newborn screening for home births.

Michigan Department of Community Health

Newborn Screening Laboratory

The Michigan Department of Community Health, Newborn Screening Laboratory is located within the Division of Chemistry and Toxicology in the Bureau of Laboratories. The mission of the Newborn Screening Laboratory Program is to provide accurate and timely testing of all Michigan newborns for evidence of eleven detectable diseases in the newborn period. Testing is available during weekdays, with additional laboratory reporting available on Saturdays. The laboratory analyzes dried blood spot filter paper specimens submitted by all Michigan birthing hospitals and midwives. More than 700 cards can be analyzed each day.

The laboratory screened for eight disorders until September of 2004. Three additional disorders were added to the panel in October 2004 with the existing tandem mass spectrometry technology, without an increase in the screening fee. The laboratory tested 134,103 specimens from 127,572 infants born in 2004.

Newborn Screening Follow-up Program

The Newborn Screening Follow-up Program, located in the Epidemiology Services Division within the Bureau of Epidemiology, oversees short-term and long-term follow-up of infants identified through the screening program. The program ensures that infants identified through the newborn screening program enter a seamless system of care including consultation with specialists, and routine care within a medical home. The program also facilitates the acquisition of medically necessary medications and formulas by affected infants and children and, consequently, collaborates with the Children's Special Health Care Services (CSHCS) Program and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) Program.

The follow-up program includes a program director, a nurse educator/coordinator, a quality assurance coordinator, an epidemiologist, and three follow-up technicians. The program director oversees the entire follow-up program, including contracts with the medical management centers. The nurse educator/coordinator conducts in-service trainings for hospital personnel and develops and disseminates educational materials about newborn screening. The quality assurance coordinator provides oversight for short-term follow-up. The epidemiologist provides oversight for long-term follow-up and long-term data system management. The follow-up technicians contact the medical management centers, primary care physicians, and families regarding infants with positive screens and respond to various calls about results.

When an infant screens positive for a condition, the Newborn Screening Laboratory notifies the Follow-up Program. The follow-up staff phone and fax one of the state-contracted medical management centers. The physician responsible for care of the newborn is also informed. Depending on the test result, rescreening may be required, a serum test may be ordered, or, rarely, immediate referral to a specialist or hospital emergency room is requested.

All strong positive results are immediately communicated to both the Follow-up Program and the appropriate medical management center. The medical management center contacts the child's physician to arrange for confirmatory testing and prompt treatment if indicated. A repeat sample will be requested for all borderline positive results.

If all tests for a specimen are negative, the results are sent to the hospital or midwife that submitted the newborn screen. The hospital or midwife then notifies the child's physician of the negative results.

Medical Management Centers

The Michigan Department of Community Health, Newborn Screening Follow-up Program contracts with three medical management centers to provide comprehensive follow-up and medical management services for infants identified through newborn screening. The three centralized centers include the Endocrine Follow-up Program at the University of Michigan Medical Center, the Children's Hospital of Michigan Metabolic Program, and the Sickle Cell Disease Association of America, Michigan Chapter.

Medical Management Centers

The Department of Community Health, Newborn Screening Program contracts with three outside agencies to provide comprehensive follow-up and medical management services.

Endocrine Follow-up Program, University of Michigan Medical Center

Since 1987, the Endocrine Follow-up Program in the Department of Pediatrics, University of Michigan, contacts all families of newborns with positive screens for hypothyroidism to arrange for appropriate diagnosis and referral for medical management of congenital hypothyroidism. The program was expanded in 1993 to include follow-up for congenital adrenal hyperplasia. In 2004, the program expanded to include a Center of Excellence for the Diagnosis and Management of Congenital Adrenal Hyperplasia, directed by Ming Chen, M.D., Ph.D.

The Endocrine Follow-up Program maintains a centralized communication, referral and treatment assessment office which provides follow-up to ensure appropriate diagnostic evaluation and treatment of all infants with positive congenital hypothyroidism or congenital adrenal hyperplasia screening test results in Michigan. The director of the program, Carol Foster, M.D. also organizes and maintains a network of pediatric endocrinologists throughout the state. The Pediatric Endocrinology Advisory Committee (PEAC) provides advice to the Michigan Newborn Screening Program on screening, diagnosis and medical management of newborn endocrine disorders.

Pediatric Neurology Metabolic Clinic, University of Michigan Medical Center

From January through September of 2004, the Pediatric Neurology Metabolic Clinic in the Department of Pediatrics at the University of Michigan was responsible for the diagnosis and medical management of newborns with metabolic disorders detected by newborn screening. The clinic housed a centralized medical management team offering both clinical consultation and laboratory diagnostic facilities for patients with inborn errors of metabolism. The services provided included diagnostic evaluation, treatment, and management for patients with phenylketonuria (PKU), galactosemia, maple syrup urine disease (MSUD), biotinidase deficiency, and medium-chain acyl-CoA dehydrogenase deficiency (MCADD), referred by the Michigan Newborn Screening Program, in addition to other neurometabolic disorders.

Children's Hospital of Michigan Metabolic Program

In October 2004, the Children's Hospital of Michigan Metabolic Program became the primary referral site for all metabolic disorders identified through newborn screening in Michigan. The

program is responsible for the diagnosis and medical management of all newborns with the eight metabolic disorders detected by newborn screening. In addition to the metabolic disease clinic, the program provides biochemical and molecular genetics diagnostic laboratory services. The program is now developing clinical and laboratory capacity for expanded newborn screening based on tandem mass spectrometry. The program is directed by Gerald Feldman, M.D., Ph.D. The clinical director is Ayesha Amhad, M.D. Robert Grier, Ph.D., is the director of the biochemical genetics laboratory.

The Division of Genetic and Metabolic Disorders at the Children's Hospital of Michigan offers comprehensive services to children and their relatives with any type of a genetic disorder. The division provides consultation for diagnosis, genetic counseling, follow-up and treatment of genetic conditions. The division also provides reports to consulting physicians and families, and educational brochures and support group information to families. The division has board-certified physicians in clinical genetics, biochemical genetics and clinical molecular genetics, and board-certified genetic counselors. The Detroit Medical Center has an excellent laboratory facility consisting of molecular genetic diagnostics and cytogenetics. The division also has a close working relationship with the Reproductive and Prenatal Genetics program at Hutzel Hospital.

Sickle Cell Disease Association of America, Michigan Chapter (SCDAA)

Since 1987, the Sickle Cell Disease Association of America has provided comprehensive services to all newborns with sickle cell hemoglobinopathies in Michigan. The SCDAA is located in Detroit and is directed by Charles Whitten, M.D. A clinical services component is at Children's Hospital of Michigan and is directed by Wanda Shurney, M.D. The primary responsibilities of the SCDAA are to assure that: (1) all newborns referred with positive sickle cell screening results are appropriately diagnosed, (2) penicillin prophylaxis is initiated, (3) sickle cell counseling and social work services are provided, and (4) each newborn has a medical home.

The goal of the SCDAA is to enable individuals with sickle cell anemia to live lives that, to the extent possible, are unhampered and uncompromised by having sickle cell anemia. Furthermore, the chapter enables individuals with the sickle cell trait to make informed decisions that they believe are in their best interest with respect to family planning. To meet these goals, the chapter provides the following services: (1) social work/patient advocates to assure that clients receive immediate and long-term medical care, (2) counseling and testing to determine whether a person is a carrier of the sickling gene, (3) public education, (4) career development for individuals with sickle cell disease, (5) tutorial program for students with sickle cell disease, and (6) support groups and parent clubs to provide support services for parents. Patient advocates are located in Grand Rapids, Benton Harbor, Pontiac, Flint, Kalamazoo, Lansing, Muskegon, and Saginaw and provide counseling to families and ensure that all identified children have a medical home.

Newborn Screening Laboratory Testing

Biotinidase Deficiency

Biotinidase deficiency testing is performed with a qualitative colormetric assay. The biotinidase test uses a synthetic biotin substrate N-biotinyl-p-aminobenzoate (B-PABA). The blood of a normal newborn contains biotinidase and, in the assay, clears the substrate to biotin and P-aminobenzoic acid (PABA). After overnight reaction of the specimen with the substrate, a clear solution is obtained by precipitation of hemoglobin proteins with strong trichloroacetic acid. Reagents are added in a timed sequence and purple color develops via a diazotization reaction of the amino groups from PABA and N-(1-naphthyl) ethylenediamine. Pale or straw color remains with the blood of a biotinidase deficient newborn because the B-PABA substrate cannot be cleared to yield PABA.

Citrullinemia and Argininosuccinic Aciduria

Citrullinemia and argininosuccinic aciduria (ASA) testing is performed with tandem mass spectrometry by evaluation of the citrulline and citrulline/tyrosine profile.

Reporting results for citrullinemia and argininosuccinic aciduria are as follows:

Citrulline Concentration $\mu\text{mol/L}$	CIT/TYR Ratio	Result Patient < 24 hours old	Result Patient \geq 24 hours old
0.1 - 53	< 1.0	Unsatisfactory	Negative
\geq 54	\geq 1.0	Strong Positive	Strong Positive

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) testing is performed with time-resolved fluorometry for 17 alpha-hydroxy progesterone (17-OHP). The procedure used in the laboratory is a quantitative determination of 17-OHP. The procedure is performed on the *AutoDELFI*A, manufactured by Wallac, Inc. It is a solid phase, time-resolved fluororoimmunoassay based on competitive binding between europium-labeled 17-OHP and sample 17-OHP for a limited number of binding sites. Enhancement solution dissociates europium ions from the labeled antibody into solution, where they form highly fluorescent chelates. The fluorescence for each sample is measured and is inversely proportional to the quantity of 17-OHP.

Reporting results for congenital adrenal hyperplasia are as follows:

17-OHP Concentration ng/ml	Result Patient <2,500 gm and/or <= 12 hours old	Result Patient >=2,500 gm and/or > 12 hours old
< 60	Negative	Negative
60 - 74	Negative	Borderline Positive
75 - 99	Negative	Strong Positive
100 - 149	Borderline Positive	Strong Positive
>= 150	Strong Positive	Strong Positive

Congenital Hypothyroidism

Congenital hypothyroidism (CH) testing is performed with time-resolved fluorometry for thyroid stimulating hormone (TSH). The TSH assay is a solid phase, two-site immunoassay manufactured by Perkin-Elmer. Europium-labeled monoclonal antibodies are directed against antigenic sites on the TSH molecule. Enhancing reagent dissociates the europium ion into a fluorescent solution which is directly proportional to the concentration of TSH in the infant's blood.

Reporting results for congenital hypothyroidism are as follows:

TSH concentration uU/mL, serum units	Result Patient < 24 hours old	Result Patient 24-26 hours old	Result Patient 27 hours- 6 days old	Result Patient 7-28 days old
<13	Unsatisfactory	Negative	Negative	Negative
13 - 24	Unsatisfactory	Negative	Negative	Borderline or Strong Positive*
25 - 32	Unsatisfactory	Negative	Borderline Positive	Borderline or Strong Positive*
33 - 49	Unsatisfactory	Borderline Positive	Borderline Positive	Borderline or Strong Positive*
<= 50	Strong Positive	Strong Positive	Strong Positive	Strong Positive

* Considered strong positive if second positive newborn screening test result

Galactosemia

Galactosemia testing is performed with a fluorometric assay for the Galactose-1-Phosphate Uridyl transferase enzyme. Abnormal samples are confirmed with a fluorometric test for total

galactose. The procedure manufactured by PerkinElmer-Wallac, Inc. is an adaptation of the Beutler and Baluda procedure. The assay is based on the enhancement of the fluorescence of NADPH through a series of enzymatic reactions. This is a quantitative method that measures the enzyme galactose-1-phosphate uridyl transferase.

A secondary test for total galactose, manufactured by PerkinElmer-Wallac, Inc. is performed on all infants with positive tests. The test is a fluorimetric assay that simultaneously measures galactose and galactose-1-phosphate. A fluorescent microplate reader and Galactose Test Kit make use of a fluorescent, galactose oxidase method in a microplate format.

Reporting results for galactosemia are as follows:

Total Galactose Concentration mg/dL	GALT U/gHb		
	≤ 2.4	2.5 - 3.0	≥ 3.1
0.1 - 14.9	Strong Positive	Borderline Positive	Negative
15.0 - 19.9	Strong Positive	Borderline Positive	Negative
≥ 20.0	Strong Positive	Borderline Positive	Negative

Homocystinuria

Homocystinuria testing is performed with tandem mass spectrometry by evaluation of methionine and methionine/phenylalanine profile.

Reporting results for homocystinuria are as follows:

Methionine Concentration $\mu\text{mol/L}$	MET/PHE Ratio	Result Patient < 24 hours old	Result Patient ≥ 24 hours old
0.1 - 86	< 1.3	Unsatisfactory	Negative
≥ 87	≥ 1.3	Strong Positive	Strong Positive

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) testing is performed with tandem mass spectrometry by evaluation of the leucine.

Reporting results for maple syrup urine disease are as follows:

Leucine Concentration $\mu\text{mol/L}$	Result Patient 0 - 8 days old	Result Patient > 8 days old
0.1 – 299	Negative	Negative
300 – 499	Strong Positive	Negative
≥ 500	Strong Positive	Strong Positive

Medium-chain Acyl-CoA Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) testing is performed with tandem mass spectrometry by evaluation of the C8 and C8/C10 acylcarnitine profile.

Reporting results for medium-chain acyl-CoA dehydrogenase deficiency are as follows:

C8 Concentration $\mu\text{mol/L}$	C8/C10 Ratio	Initial Result	Repeat Patient Result
0.1 - 0.42	< 6.0	Negative	Unsatisfactory
≥ 0.43	≥ 6.0	Strong Positive	Strong Positive

Phenylketonuria

Phenylketonuria (PKU) testing is performed with tandem mass spectrometry by evaluation of the phenylalanine and phenylalanine/tyrosine profile.

Reporting results for phenylketonuria are as follows:

Phenylalanine Concentration $\mu\text{mol/L}$	PHE/TYR Ratio	Result
0.1 – 133	< 2.1	Negative
134 – 179	≥ 2.1	Borderline Positive
≥ 180	≥ 2.1	Strong Positive

Sickle Cell Disease and Other Hemoglobinopathies

Sickle cell disease and other hemoglobinopathies are determined by high performance liquid chromatography (HPLC) manufactured by Bio-Rad. Abnormal results are confirmed by isoelectric focusing (IEF). During this procedure, the hemoglobins are separated by ionic strength. The blood spot eluate is injected into the carrier solvent, which flows to the column. The different hemoglobins are attracted to the column for different lengths of time as an

increasingly cationic solution is passed over them. The released hemoglobins are detected by a visible wavelength absorbance detector. By comparing variants to controls, different hemoglobins are identified.

Those patients with hemoglobin variants detected by HPLC are retested by isoelectric focusing (IEF) manufactured by PerkinElmer-Wallac, Inc. In this method, the variants migrate characteristic distances based on their isoelectric points (pI's). This migration takes place in the presence of an electric current through an ampholyte-filled agarose gel. After resolution is achieved, the hemoglobins are affixed to the gel and stained. Comparison with controls gives identification of major hemoglobins.

Newborn Screening Laboratory Cut-Off Values for Analytes by Disorder as Reported to Physicians

Disorder	Analyte	Expected Result
Congenital Adrenal Hyperplasia	17-OHP	< 60 ng/mL
Congenital Hyperthyroidism	TSH	* varies with age
Galactosemia	GALT	> 3.1 U/gHb
Maple Syrup Urine Disease	Leucine	< 300 umol/L
Phenylketonuria	Phenylalanine	< 134 umol/L
MCADD	Acylcarnitine(s)	Normal Profile
Hemoglobinopathy	Hemoglobin	Normal Pattern
Biotinidase Deficiency	Biotinidase	Normal Activitiy
Homocystinuria	Methioine	< 87 umol/L
Citrullinemia	Citrulline	< 54 uml/L
Arginonosuccinic Aciduria	Citrulline	< 54 umol/L

* Abnormal Result (uIU/mL); <24h, not defined; 24-36h, <33; 37h-6d, <25; 7d-31d, <13; > 31d, <=10

Description of Newborn Screening Disorders

Biotinidase Deficiency

Biotinidase deficiency is an autosomal recessive disorder that interferes with the body's ability to synthesize biotin, a B vitamin. Biotinidase is an enzyme responsible for recycling biotin in the degradation of carboxylases, as well as freeing the protein-bound form in digestion. Biotin is an essential co-factor in several metabolic pathways, the deficiency of which ultimately results in neurologic damage. The incidence of Biotinidase Deficiency in Michigan is one in 27,325 births. This includes profound and partial deficiencies.

Biotinidase enzyme activity is detected by a colorimetric assay. Transfusion of whole blood may interfere with the accuracy of testing, causing a false negative result. It is recommended that the newborn screen be obtained before a transfusion is initiated.

All strong and persistent borderline positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) for follow-up and diagnosis. Daily oral biotin supplementation is successful in preventing sequelae in those who are asymptomatic prior to initiation of treatment.

Citrullinemia and Argininosuccinic Aciduria

Citrullinemia and argininosuccinic aciduria (ASA) are rare disorders of the urea cycle. Citrullinemia is caused by excess citrulline and ammonia in the blood resulting from a deficiency of argininosuccinic acid synthetase activity. Argininosuccinic aciduria is the result of excess argininosuccinic acid, citrulline, and ammonia in the blood due to a deficiency of argininosuccinic acid lyase enzyme activity. The estimated incidence of these disorders in Michigan is one in 250,000. Screening for citrullinemia and ASA began October 1, 2004.

Tandem mass spectrometry is used to detect elevated levels of citrulline. The newborn screening test detects elevated citrulline but cannot differentiate citrullinemia from argininosuccinic aciduria. Further diagnostic testing is needed. Test results are valid once the infant has reached 24 hours of age.

Immediate contact is made with the CHMMC for follow-up and diagnosis.

The treatment for citrullinemia and argininosuccinic aciduria includes a high-calorie diet restricting protein. Arginine supplementation, as well as administration of sodium benzoate and sodium phenylacetate is also initiated. Certain individuals may require dialysis.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a family of inherited autosomal recessive disorders of adrenal steroidogenesis. It results from a defect in any of the five enzymes needed to synthesize cortisol from cholesterol in the adrenal gland, but about 80% of all cases are due to deficiency of the enzyme 21-hydroxylase (21-OH). About 15% of cases are due to 11 β -hydroxylase deficiency. The goal of newborn screening for CAH is to rapidly identify affected infants to prevent death from adrenal crisis, shock or its sequelae, and incorrect sex assignment in female newborns. The incidence of this disorder in Michigan is one in 17,716 births.

Fluoroimmunoassay is used to detect elevated 17-hydroxyprogesterone (OHP). Interpretation of values is based on birth weight and age at the time of specimen collection. False positive results may occur if the sample is collected before 24-hours of age. Chronic use of dexamethasone in the mother during pregnancy can depress 17-OHP levels, which can cause a false negative result in an affected newborn. All strong and persistent borderline positive tests are referred to the Endocrine Follow-up Program (EFUP) at the University of Michigan. The EFUP coordinates follow-up for infants with suspected CAH. Glucocorticoid is used to replace deficient cortisol while suppressing ACTH overproduction. Salt-retaining hormones may be used. Early intervention and surgical correction of ambiguous genitalia allow normal puberty, fertility and childbearing in females. Careful regulation of hormone treatment during illness and growth periods is required.

Congenital Hypothyroidism

Congenital hypothyroidism (CH) occurs in babies who do not have the ability to produce adequate amounts of thyroid hormone. Most cases are sporadic, but it occasionally occurs in siblings and may be inherited as an autosomal recessive disorder. The most common causes of primary hypothyroidism include: thyroid gland aplasia or hypoplasia, ectopic thyroid gland, or enzyme deficiencies in thyroxine (T4) synthesis. Less commonly, hypothyroidism is induced by medications (antithyroid drugs or excess iodine) in the mother. The incidence of this disorder in Michigan is one in 1,942 births.

A fluorometric assay laboratory test screens for elevations of TSH (thyrotropin). False positive results can occur on specimens obtained before 24 hours of age due to the normal physiologic TSH surge that occurs after birth.

All strong and persistent borderline positive tests are referred to the EFUP at the University of Michigan. The EFUP coordinates follow-up for infants with suspected CH. Diagnosis and treatment is provided through a network of pediatric endocrinologists throughout the state.

Treatment consists of oral thyroid hormone (replacement) administered daily. This should begin as soon as possible after confirmation of the diagnosis.

It is important to note that most, but not all, cases of severe, early onset hypothyroidism are detected by newborn screening. The screening program is not designed to detect late onset, clinically moderate or sub-clinical forms of hypothyroidism. The newborn screen should not be relied on to rule out all abnormalities of thyroid function.

Galactosemia

Galactosemia is an inherited autosomal recessive disorder of carbohydrate metabolism. Classic galactosemia is due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase, which leads to an accumulation of total galactose. In nature, galactose is combined with glucose to form lactose, the primary sugar in human milk and commercial (non-soy) infant formulas. Affected infants are not able to metabolize lactose, causing the build-up of galactose in the body, which can lead to cellular damage and even death. There are several benign genetic variants characterized by a less severe reduction in enzyme activity (e.g., Duarte variant). These children often present with a persistent positive newborn screen but are asymptomatic. There is some controversy over treatment of Duarte (DG) variants. In Michigan, these infants are treated for one year with soy formula. The incidence of this disorder in Michigan is one in 41,227 births.

Quantitative GALT enzyme screening is done on all infants. Quantitative fluorometric assay to detect Galactose + galactose-1-phosphate (total galactose) is done on all infants with positive tests and or records of transfusion. Transfusion of red blood cells may interfere with the accuracy of the test causing a false negative result. It is recommended that the newborn screen be obtained before a transfusion is initiated. All strong and persistent borderline positive tests are referred to the CHMMC for follow-up and diagnosis. Treatment is initiated by the immediate change to soy/lactose free formula with subsequent lifelong exclusion of galactose from the diet.

Homocystinuria

Homocystinuria is a rare disorder caused by cystathionine *B*-synthase (CBS) deficiency. Deficiency of CBS, a pyridoxine (vitamin B6) dependent enzyme, will result in elevations of homocysteine and methionine. The purpose of newborn screening for homocystinuria is to identify affected infants rapidly and to initiate treatment to prevent/minimize disease sequelae. The estimated incidence of this disorder in Michigan is one in 200,000 births. Screening for homocystinuria began October 1, 2004.

Tandem mass spectrometry is used to detect elevated levels of methionine. All strong and persistent borderline positives are referred to the CHMMC.

Dietary restriction of methionine should be initiated. Supplemental cystine and betaine may be given. Pyridoxine supplements benefit many children, and folic acid as well as vitamin B12 supplements may be initiated.

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is a rare inherited autosomal recessive disorder. Newborns with MSUD have a deficiency of the enzyme, branched-chain ketoacid dehydrogenase, responsible for metabolizing the branched chain amino acids leucine, isoleucine, and valine found in protein. The purpose of newborn screening for maple syrup urine disease is to identify affected infants rapidly, and initiate treatment to prevent neurological sequelae and death. The incidence of this disorder in Michigan is one in 234,992 births.

Immediate treatment with free or reduced branched-chain amino acid formula is necessary. Specially prepared branched-chain-free parenteral nutrition is available for acutely ill infants. Long-term treatment consists of a strict diet limiting the intake of branched chain amino acids while maintaining normal growth and development.

Medium Chain Acyl-CoA Dehydrogenase Deficiency

Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive fatty acid oxidation disorder (FOD) in which an enzyme defect in the fatty acid metabolic pathway inhibits the body's ability to utilize stored fat. Clinical symptoms include vomiting and lethargy following a period of fasting, often at times of intercurrent viral infection (gastrointestinal or upper respiratory). Hypoglycemia with low urinary ketone production (hypoketotic), hyperammonemia and elevated liver function tests may occur and can lead to encephalopathy, hepatic failure, coma or death.

All strong and persistent borderline positive tests are referred to the CHMMC for follow-up and diagnosis.

Strict avoidance of fasting (frequent feedings) is essential. A low-fat/high-carbohydrate diet and supplemental carnitine are often used. Acute episodes (during illness) require aggressive medical management, especially if the infant/child is vomiting or is not receiving adequate nutritional intake. During these episodes, the administration of intravenous glucose and blood sugar monitoring is essential.

Phenylketonuria

Phenylketonuria (PKU) is an inherited autosomal recessive disorder, which prevents the body from using the amino acid phenylalanine (Phe) properly. It is caused by a deficiency of the liver enzyme phenylalanine hydroxylase. Variant forms are caused by impaired synthesis or recycling of the bipterin (BH4) cofactor. Early detection and treatment is imperative to prevent mental retardation. The incidence of this disorder in Michigan is one in 8,801 births. This includes classic PKU, mild PKU, and non-PKU hyperphenylalaninemia.

Tandem mass spectrometry is used to determine elevated levels of phenylalanine and the phenylalanine/tyrosine ratio.

All strong and persistent borderline positive tests are referred to the CCHMMC for follow-up and diagnosis.

Sickle Cell Disease and Other Hemoglobinopathies

There are over 600 hemoglobin variants, however only a few are clinically significant. The clinically significant hemoglobinopathies are inherited autosomal recessive disorders of the adult β -hemoglobin chain. Children with two abnormal β -globin genes (homozygotes or double heterozygotes) have a hemoglobin disease whereas those with only one abnormal gene are said to have hemoglobin trait, which is only of genetic significance. The purpose of newborn screening for hemoglobinopathies is to prevent deaths from pneumococcal sepsis by instituting penicillin prophylaxis. The incidence of this disorder in Michigan is one in 1,956 births. This number increases in African American newborns to about one in 600 births. This disorder is also seen in individuals of Mediterranean, Indian and Middle Eastern heritage.

High performance liquid chromatography (HPLC) detects abnormal hemoglobins S, C, D, and E. A secondary method is by isoelectric focusing. The test is invalid on transfused infants. It is important to obtain the newborn screen before transfusion. A retest is required three months after the most recent transfusion. Infants with positive sickle-related screening tests are referred to the Sickle Cell Disease Association of America (SCDAA), Michigan Chapter for confirmatory diagnosis and follow-up. Penicillin prophylaxis should begin as soon as possible and continue until the child is six years old. It is important to note that the purpose of the newborn hemoglobinopathy-screening program is to identify infants with sickle cell-related conditions. The responsibility for the follow-up of infants found to have non-sickle cell-related hemoglobinopathies is left to the discretion of the physician of record.

Quality Assurance

Data Management

The Newborn Screening Program supports a full-time quality assurance coordinator to provide program evaluation by monitoring data from hospitals, the newborn screening laboratory, and the medical management centers. The coordinator uses the PerkinElmer, Patient Care module, with data derived from the PerkinElmer Life Cycle module for follow-up of positive, unsatisfactory and early newborn screening cases. The Patient Care module is used as a tracking tool to follow all positive newborn screening tests until final confirmation is made. If the infant has a final confirmation of normal, that case is closed in the database. If the infant is diagnosed with a newborn screening disorder, the case will still be closed in the laboratory database with the diagnosis noted. All data on that infant are imported into a medical management database for long-term follow-up. While PerkinElmer has provided general manuals for using the module, over the past year the quality assurance coordinator developed specific training manuals for newborn screening follow-up staff.

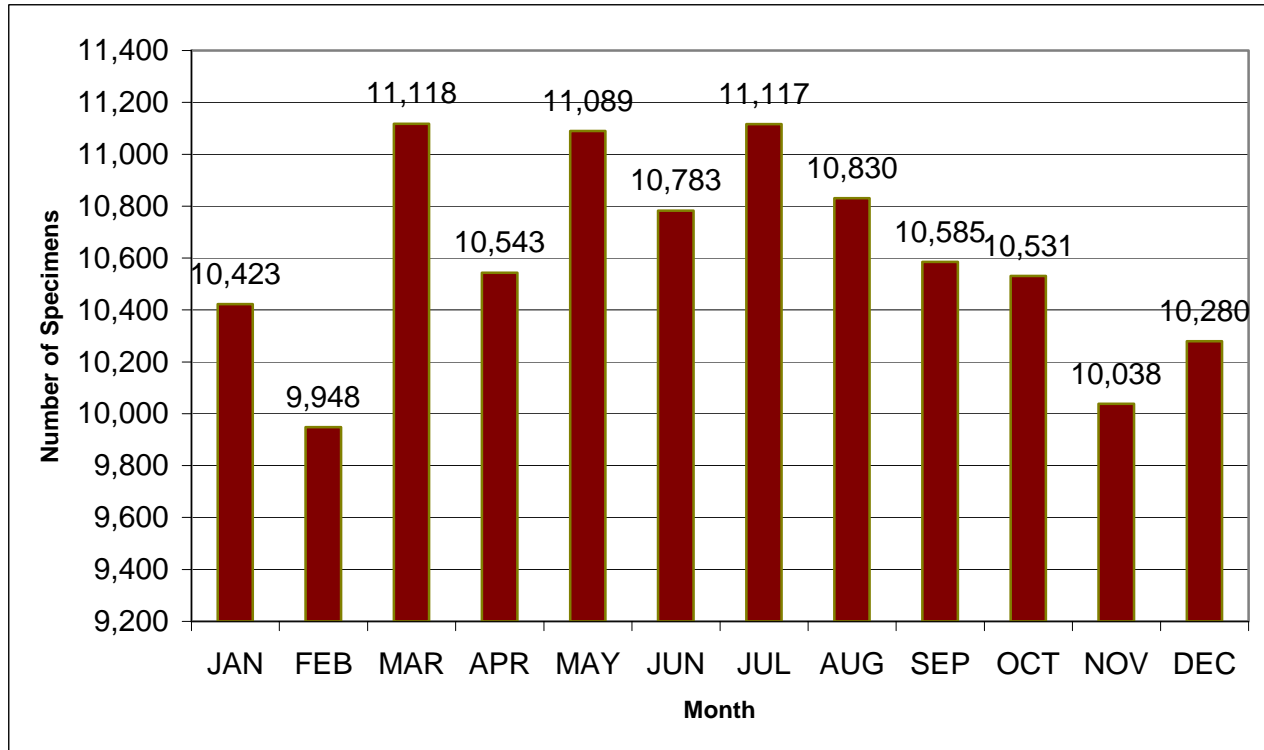
The coordinator, in collaboration with PerkinElmer, the Michigan Department of Information Technology, and local information technology specialists, is currently installing the Patient Care module at the three medical management centers. The module will be accessed through Virtual Private Networks (VPNs). The coordinator is also developing manuals specific to these medical management follow-up groups, and will provide primary support for the Patient Care module at the centers.

Quality Assurance Notification to Birthing Hospitals

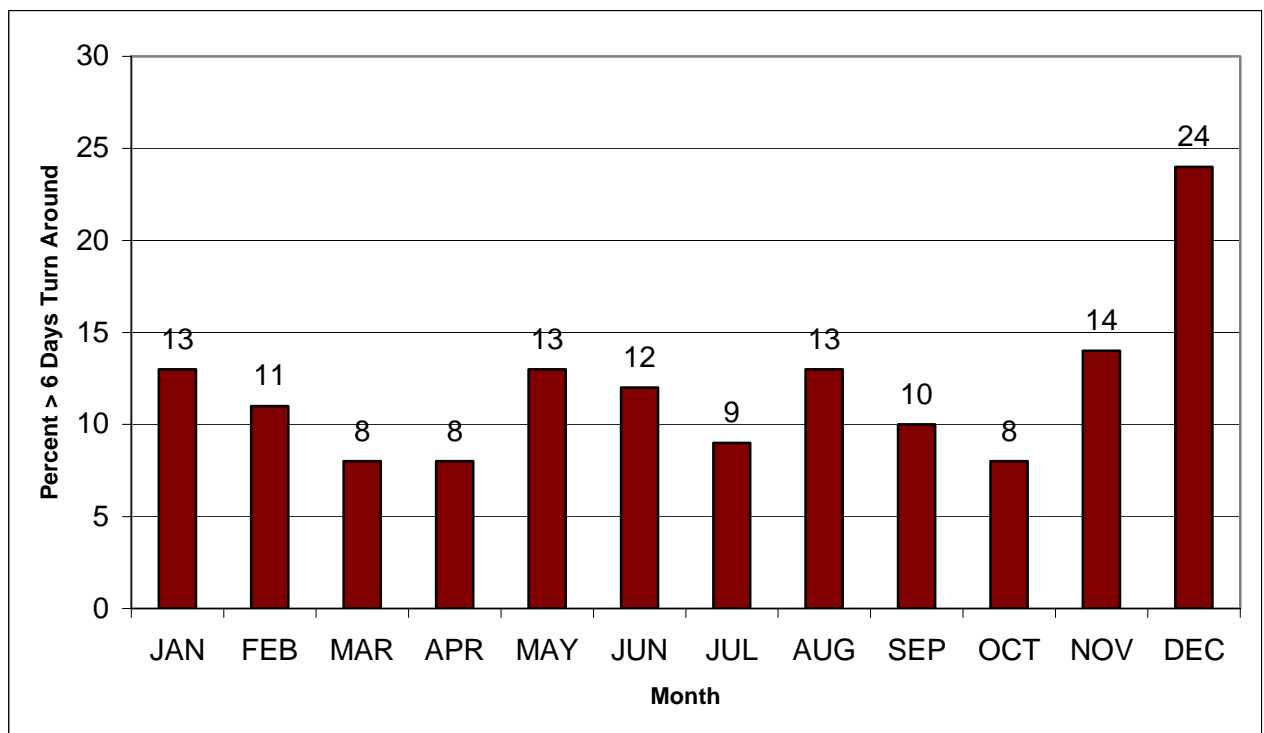
The quality assurance coordinator also provides quarterly reports to all birthing hospitals in Michigan. The quarterly reports, titled *Quality Assurance Notification*, provide data on specimen turnaround time, the number of unsatisfactory specimens, the number of specimens missing essential information, such as birth weight, and any data necessary to calculate the age of the infant, such as specimen date. The report provides monthly and quarterly data for individual hospitals and for the state as a measure for comparison. The statewide percent of unsatisfactory specimens ranged from one to three percent throughout 2004. See the following tables for additional quality assurance data.

The *Quality Assurance Notification* is provided to hospitals to help them monitor their hospital's newborn screening performance. The quarterly report can be shared with staff during routine staff meetings or at inservices. Management can demonstrate to staff areas that need improvement, such as incomplete information documented on the newborn screening card, unsatisfactory specimens, and excessive turnaround time. The unit manager can also provide staff with examples when the quality of their newborn screening process has improved.

Number of Specimens Received from Birthing Hospitals by Month, 2004



Percent of Specimens Received from Birthing Hospitals Greater than 6 Days After Birth by Month, 2004



Epidemiology of Newborn Screening in Michigan, 2004

Summary of Confirmed Cases Detected by Newborn Screening Program, Michigan Department of Community Health, 2004

CONDITION	YEAR SCREENING BEGAN	DIAGNOSED CASES, 2004	TOTAL CASES THROUGH 2004
Phenylketonuria (PKU)	1965	12	543
Congenital Hypothyroidism (CH)	1977	66	1,183
Galactosemia	1984	2	61
Sickle Cell Disease	1987	74*	1,243
Maple Syrup Urine Disease (MSUD)	1987	2	12
Biotinidase Deficiency	1987	23	112
Congenital Adrenal Hyperplasia (CAH)	1993	8	99
MCADD	2003	6	11
Homocystinuria	2004	0	0
Citrullinemia/ASA	2004	0	0
TOTAL	1965-2004	193	3,264

* Includes both presumptive positive and confirmed positive cases.

Note that in 2004, there were 14 strong positive results for homocystinuria and two strong positive results for citrullinemia/ASA.

Biotinidase Deficiency

Newborn Screening Results for Cases of Biotinidase Deficiency, Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>			TOTAL
	Profound	Partial	Normal	
Strong +	1	1	2	4
Borderline +	0	21	407	428
TOTAL	1	22	409	432

Characteristics of Infants Identified with Profound and Partial Biotinidase Deficiency, Michigan, 2004

	<u>Profound</u>	<u>Partial</u>
Sex		
Female	0	11
Male	1	11
Unknown	0	0
Race		
White	1	18
Black	0	2
American Indian	0	0
Asian/Pacific	0	0
Islander		
Middle Eastern	0	0
Multi-Racial	0	0
Unknown	0	2
Minimum Days to Treatment*	14	6
Maximum Days to Treatment*	14	61
Mean Days to Treatment*	14	37

* From day of birth

Number of infants diagnosed with profound biotinidase deficiency 1987-2004:	17
Number of infants diagnosed with partial biotinidase deficiency 1987-2004:	95
TOTAL number of infants diagnosed with biotinidase deficiency 1987-2004:	112

Congenital Adrenal Hyperplasia

Newborn Screening Results for Cases of Congenital Adrenal Hyperplasia (CAH), Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>		Normal	TOTAL
	Salt-Wasting	Non-Salt- Wasting		
Strong +	4	3	70	77
Borderline +	0	1	241	242
TOTAL	4	4	311	319

Characteristics of Infants Identified with Confirmed Congenital Adrenal Hyperplasia, Michigan, 2004

	<u>Salt-Wasting</u>	<u>Non-Salt-Wasting</u>
Sex		
Female	1	0
Male	3	4
Unknown	0	0
Race		
White	3	2
Black	0	0
American Indian	0	0
Asian/Pacific	0	0
Islander		
Middle Eastern	1	0
Multi-Racial	0	1
Unknown	0	1
Minimum Days to Treatment*	6	8
Maximum Days to Treatment*	14	47
Mean Days to Treatment*	9	23

* From day of birth

Number of infants diagnosed with salt wasting CAH 1987-2004:	76
Number of infants diagnosed with non-salt wasting CAH 1987-2004:	23
TOTAL number of infants diagnosed with CAH 1987-2004:	99

Congenital Hypothyroidism

Newborn Screening Results for Cases of Congenital Hypothyroidism, Michigan Department of Community Health, 2004

<u>Confirmatory Test</u>					
<u>Screening Test</u>	Scan Abnormal	Scan Normal	No Scan	Normal	TOTAL
Strong +	6	2	47	121	176
Borderline +	2	0	9	1,162	1,173
TOTAL	8	2	56	1,283	1,349

Characteristics of Infants Identified with Congenital Hypothyroidism, Michigan, 2004

	<u>Abnormal Scan^a</u>	<u>Normal Scan</u>	<u>No Scan</u>
Sex			
Female	6	2	28
Male	2	0	28
Unknown	0	0	0
Race			
White	5	0	35
Black	2	0	8
American Indian	0	0	0
Asian/Pacific	0	0	0
Islander			
Middle Eastern	0	0	2
Multi-Racial	0	0	3
Unknown	1	2	8
Minimum Days to Treatment*	5		2
Maximum Days to Treatment*	23		114
Mean Days to Treatment*	11		20

^a Includes diagnoses of one aplasia, two ectopic, two lingual, two dysmorphogenesis, and one hypertrapping gland

* From day of birth

TOTAL number of infants diagnosed with hypothyroidism 1977-2004: 1,183

Galactosemia

Newborn Screening Results for Cases of Galactosemia, Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>				TOTAL
	Classic	Variant	Other Genotype	Normal	
Strong +	2	13	7	16	38
Borderline +	0	14	8	45	67
TOTAL	2	27	15	61	105

Characteristics of Infants Identified with Confirmed Galactosemia, Michigan, 2004

	<u>Classic</u>	<u>Variant^a</u>	<u>Other Genotype^a</u>
Sex			
Female	1	14	9
Male	1	13	4
Unknown	0	0	2
Race			
White	2	22	9
Black	0	1	5
American Indian	0	0	0
Asian/Pacific	0	0	0
Islander			
Middle Eastern	0	0	0
Multi-Racial	0	1	0
Unknown	0	3	1
Minimum Days to Treatment*	4		
Maximum Days to Treatment*	7		
Mean Days to Treatment*	5		

* From day of birth

^a Approximately half did not receive treatment

TOTAL number of infants diagnosed with classic galactosemia 1985-2004: 61

Hemoglobinopathies

Newborn Screening Results for Cases of Hemoglobinopathies, Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>							TOTAL
	FS	SF	FSA	SFA	FAS	ASF	AS	
FS	17	6	2	1	0	0	0	26
FSA	0	0	1	1	3	2	2	9
FSC	0	0	0	0	0	0	0	0
FSE	0	0	0	0	0	0	0	0
FSV	0	0	0	0	0	0	1	1
TOTAL	17	6	3	2	3	2	3	36

<u>Screening Test</u>	<u>Confirmatory Test</u>							TOTAL
	FSC	FCS	CSF	SCF	FSE	HPFH	Unknown	
FS	0	0	0	0	0	2	9	11
FSA	0	0	0	0	0	0	6	6
FSC	7	4	1	1	0	0	6	19
FSE	0	0	0	0	1	0	0	1
FSV	0	0	0	0	0	0	1	1
TOTAL	7	4	1	1	1	2	22	38

Maple Syrup Urine Disease

Newborn Screening Results for Cases of Maple Syrup Urine Disease, Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>		TOTAL
	Positive	Normal	
Strong +	0	18	18
Borderline +	2	92	94
TOTAL	2	110	112

Characteristics of Infants Identified with Confirmed MSUD, Michigan, 2004

	<u>MSUD</u>
Sex	
Female	2
Male	0
Unknown	0
Race	
White	1
Black	1
American Indian	0
Asian/Pacific	0
Islander	
Middle Eastern	0
Multi-Racial	0
Unknown	0
Minimum Days to Treatment*	8
Maximum Days to Treatment*	11
Mean Days to Treatment*	10

* Days from day of birth

TOTAL number of infants diagnosed with MSUD 1987-2004: 12

MCADD

Newborn Screening Results for Cases of Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD), Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>		TOTAL
	Positive	Normal	
Strong +	6	9	15
TOTAL	6	9	15

Characteristics of Infants Identified with Confirmed MCADD, Michigan, 2004

	<u>MCADD</u>
Sex	
Female	4
Male	2
Unknown	0
Race	
White	4
Black	0
American Indian	0
Asian/Pacific	0
Islander	
Middle Eastern	1
Multi-Racial	0
Unknown	1
Minimum Days to Treatment*	6
Maximum Days to Treatment*	19
Mean Days to Treatment*	12

* Days from day of birth

TOTAL number of infants diagnosed with MCADD 2003-2004: 11

Phenylketonuria

Newborn Screening Results for Cases of Phenylketonuria (PKU), Michigan Department of Community Health, 2004

<u>Screening Test</u>	<u>Confirmatory Test</u>					TOTAL
	Classic	Mild	Hyperphe ^a	BH4 ^b	Normal	
Strong +	3	2	5	1	20	31
Borderline +	0	0	1	0	22	23
TOTAL	3	2	6	1	42	54

^a Non-PKU Hyperphenylalaninemia

^b BH4 Deficiency (PTPS Defect)

Characteristics of Infants Identified with Confirmed PKU, Michigan, 2004

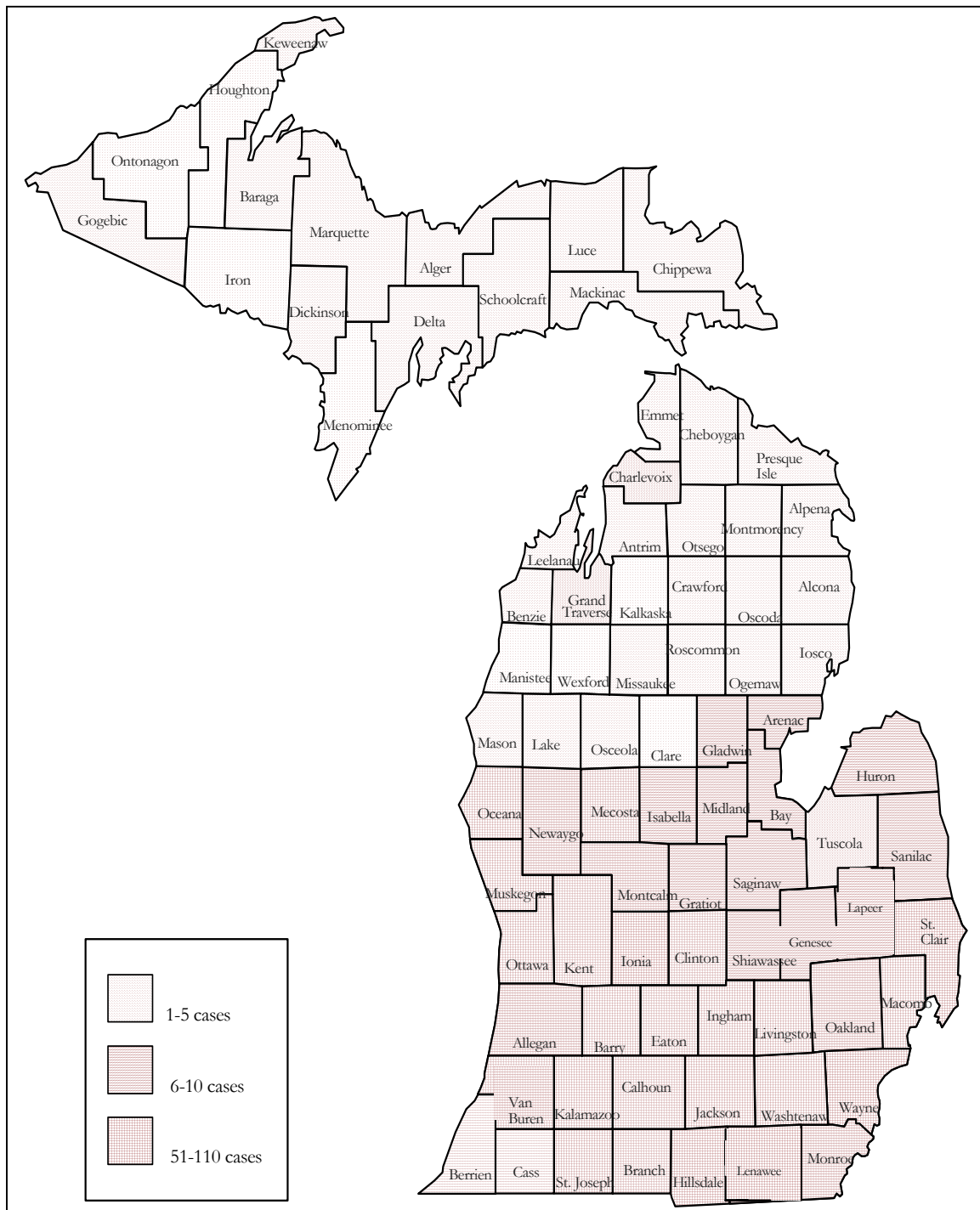
	<u>Classic</u>	<u>Mild</u>	<u>Hyperphe^c</u>	<u>BH4^c</u>
Sex				
Female	2	1	2	0
Male	2	1	3	1
Unknown	0	0	0	0
Race				
White	1	1	3	1
Black	1	0	0	0
American Indian	0	0	0	0
Asian/Pacific Islander	0	0	0	0
Middle Eastern	1	0	0	0
Multi-Racial	0	0	1	0
Unknown	1	1	1	0
Minimum Time to Treatment	7	7		
Maximum Time to Treatment	8	11		
Mean Time to Treatment	8	9		

* Days from day of birth

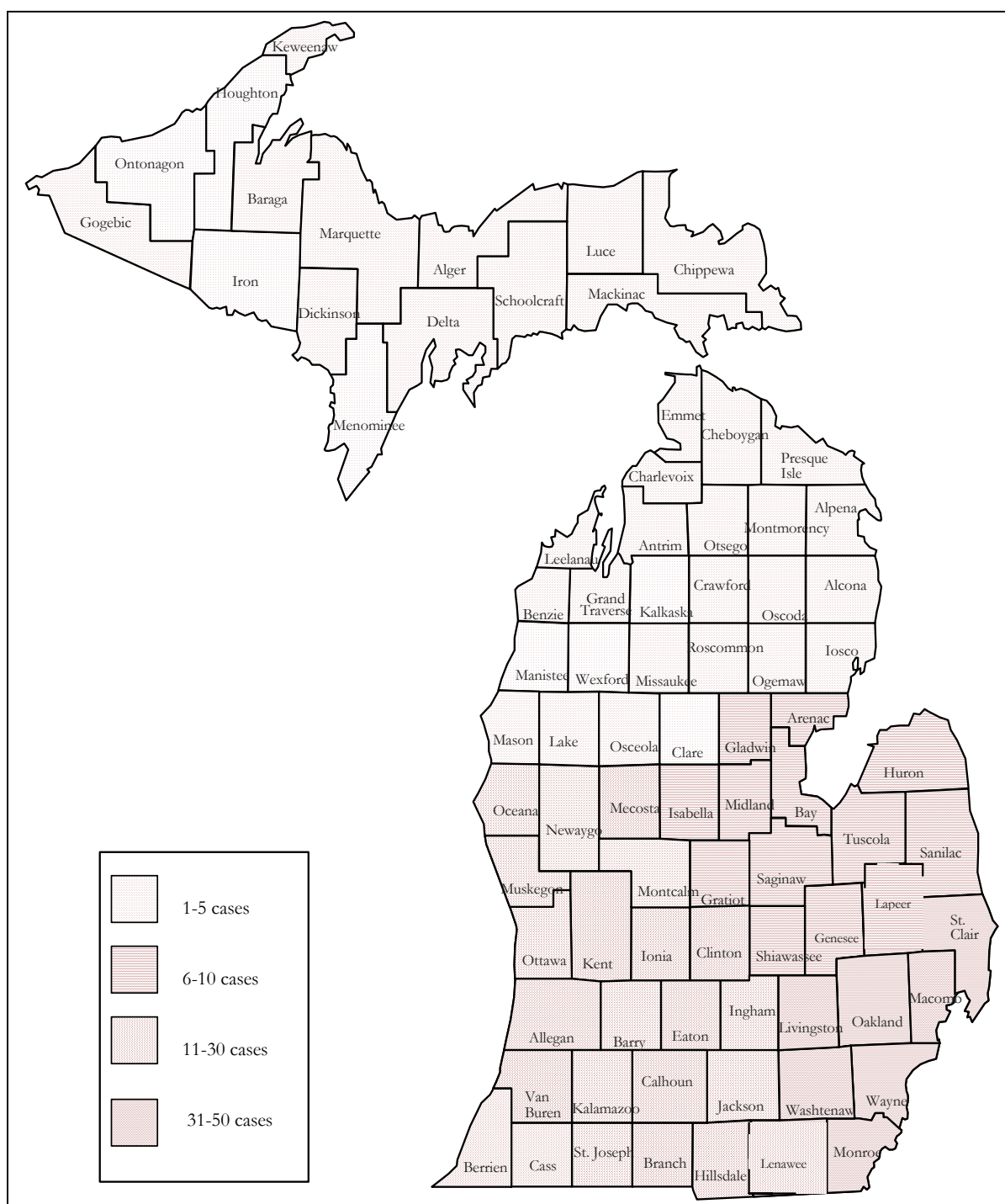
^c Approximately half did not receive treatment

Number of infants diagnosed with classic PKU 1965-2004:	189
Number of infants diagnosed with mild PKU 1965-2004:	97
Number of infants diagnosed with non-PKU hyperphenylalaninemia 1965-2004:	252
Number of infants diagnosed with BH4 deficiency 1965-2004:	5
TOTAL number of infants diagnosed with PKU-related diagnosis:	543

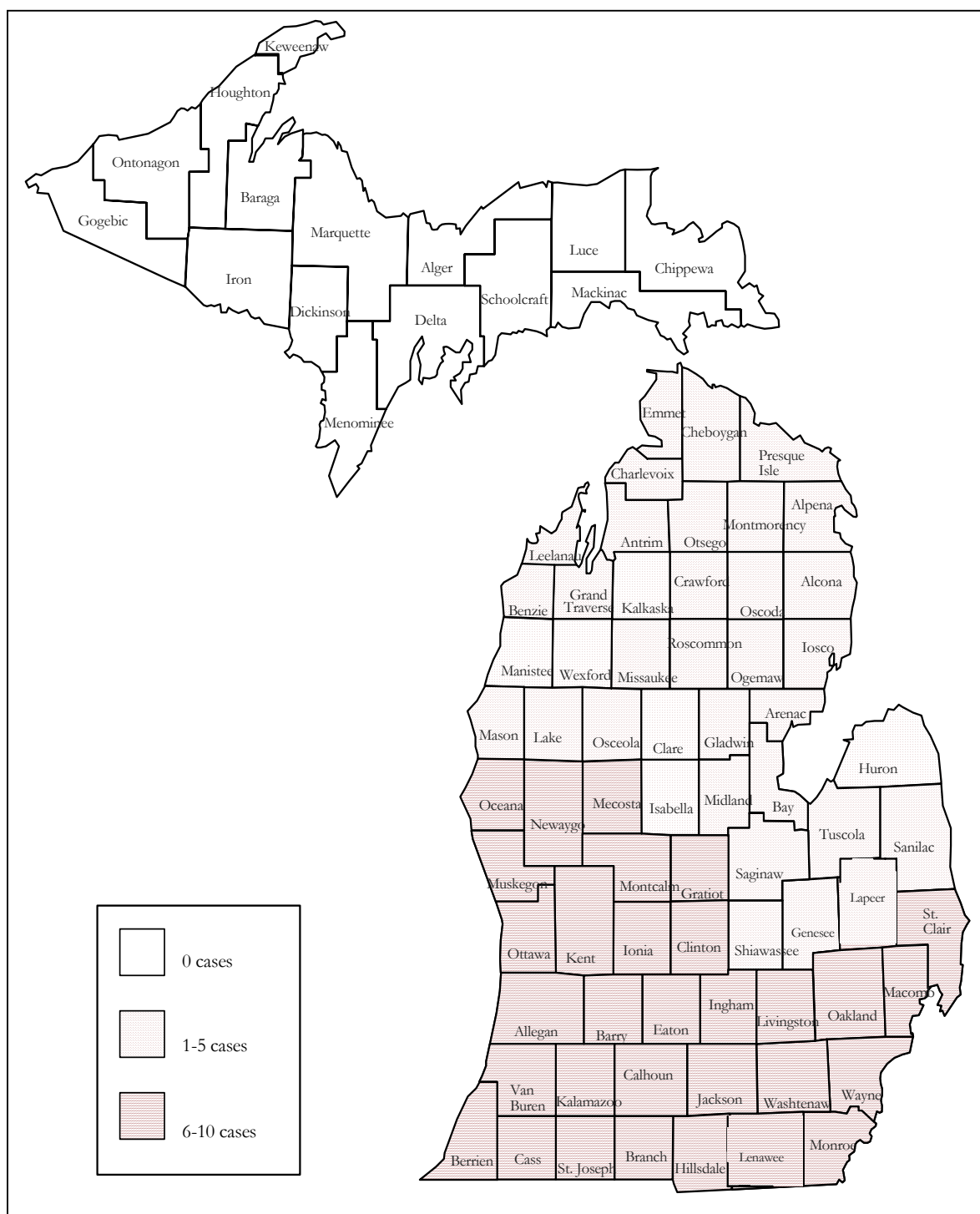
Location of Total Cases Identified by Newborn Screening by Region, 2004



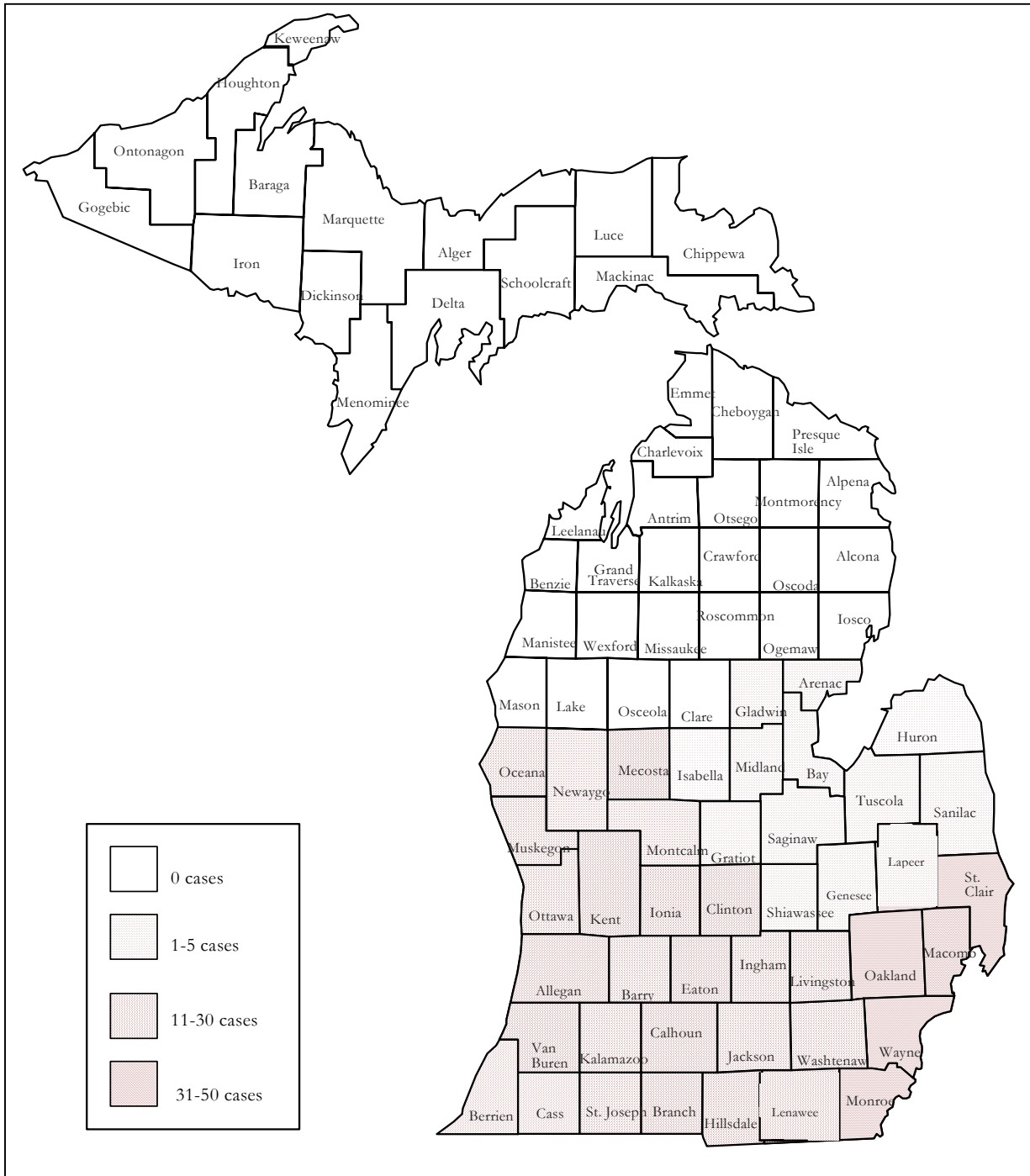
Location of Endocrine Cases Identified by Newborn Screening by Region, 2004



Location of Metabolic Cases Identified by Newborn Screening by Region, 2004



Location of Hemoglobinopathy Cases Identified by Newborn Screening by Region, 2004



Family Activities in 2004

The Newborn Screening Program supported many family activities in 2004. The program supports a part-time parent consultant, Ms. Sandy LaPrad, to support all families of newly diagnosed infants. In addition, the parent consultant is developing informational packets for families of newly diagnosed infants and a biannual family newsletter, planning family activities, and advising the newborn screening program through meetings with staff and the Newborn Screening Advisory Committee.

A brief summary of family activities in 2004 follows

- A **metabolic family activities survey** was conducted with all known families of children with a metabolic condition identified through newborn screening. The 12 families who responded to the mailed questionnaire indicated that they would like to have educational sessions as well as social activities, and are willing to travel to participate. Accordingly, some of these activities have already been organized by the parent consultant with more planned during 2005 to meet a variety of needs.
- Three **informational meetings about the new Children's Hospital of Michigan Metabolic Clinic** were held prior to the metabolic clinic move to Detroit from Ann Arbor, enabling families to meet the new clinic staff and learn more about follow-up services. The meetings were scheduled in Detroit, Lansing, and Grand Rapids.
- The **annual summer picnic** was held in July and was well attended by many families of children with metabolic conditions.
- The first meeting of the **Newborn Screening Family Advisory Committee** occurred on October 18 at Children's Hospital of Michigan. This meeting was held in Detroit so that families could meet the clinic staff and tour the new clinic. The committee will be formalized as a subcommittee of the Newborn Screening Advisory Committee and plans to meet quarterly at locations throughout Michigan. The family advisory committee designated three subcommittees focusing on policy and legislation, social activities, and education.

Topics of concern to families included (1) directions and expectations for their first visit to the new clinic, (2) concerns about contacting new clinic staff in case of a medical emergency, (3) continuation of dried blood spot monitoring for PKU and MSUD families, (4) quality improvement for the newborn screening program (e.g., quicker turnaround time), (5) and methods of including families with differing concerns due to type of disorder, age of child, etc.

- The Newborn Screening Program partnered with Children's Special Health Care Services to provide a **Parent Consultant Training** for families of children identified through newborn screening. The training was held in Lansing on November 13 and 14. Six parents attended the weekend event, representing six metabolic conditions. The parent consultants were trained to provide consultation as resource individuals for other families affected by conditions identified through newborn screening.
- Sandy LaPrad, the lead parent consultant, initiated contact with four local college instructors of obstetrics and gynecology, as well as a prenatal educators, and has developed a PowerPoint presentation for use in **discussing newborn screening with prenatal care providers**.
- A **cooking day for families with children with MSUD and PKU** was held in December in Adrian, targeting children over nine years of age. The goal of the course is to help older children learn to prepare meals in consideration of their special diets. Taste Connections owner Malathy Ramanujam taught this class.

Michigan Newborn Screening Advisory Committee

The Michigan Newborn Screening Advisory Committee is a subcommittee of the Genetic Disease Advisory Committee, which was formed in 1979 by the Michigan Department of Public Health. The mission of the committee is to advise the Michigan Department of Community Health regarding public health policies in establishing comprehensive newborn screening services. The committee meets quarterly at locations throughout the state. The specific goals of the committee include

- Review of current newborn screening practices
- Consideration of the addition of new screening tests
- Solicitation of community input with regard to newborn screening
- Evaluation of the newborn screening program infrastructure, policies and outcomes
- Recommendations to the MDCH regarding best practices in newborn screening

Committee Members

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Committee Chair
Neonatologist
Oakwood Hospital

Ayehsa Ahmad, M.D., F.A.C.M.G.
Clinical Geneticist
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Special Activities in 2004

Linking Newborn Screening and Birth Certificate Records

The Newborn Screening Follow-up Program has hired an analyst to develop algorithms to electronically match the newborn screening database and birth record files. Currently, there are sixty-eight algorithms combined in a single computer program to provide electronic matching capability. There is no common identifier between the newborn screening and birth certificate records. Errors in the newborn screening database due to difficulty reading information provided on the screening cards and/or changes in names between the time the blood is drawn for the newborn screening test and the time the birth certificate is completed results in an onerous data matching process.

The Newborn Screening Program is piloting a formal protocol for using the linked data, including manual checks of the newborn screening files for missed cases, and follow-up calls to hospitals to verify whether a specimen was submitted. In the case of hospital births that appear to have been missed, the nurse educator will receive a log of those cases so that she can problem-solve with specific hospitals as she examines their newborn screening protocols during site visits. The program plans to implement the linkage routinely, as a systematic quality assurance procedure.

Presentations by Newborn Screening Staff at the 2004 Newborn Screening and Genetic Testing Symposium, May 3-6, 2004, Atlanta, Georgia

Redefining Cut-Off Points for Congenital Hypothyroidism in Michigan

R. A. Malouin, W. I. Young, D. Pleger, K. Andruszewski, H. Hawkins, K. Cavanagh, Michigan Department of Community Health, Lansing, MI and C. M. Foster, University of Michigan Medical Center, Ann Arbor, MI

The 2000 National Newborn Screening Report revealed that Michigan had the highest number (6,401) and second highest incidence (1:21) of “Not Normal” hypothyroid screens in the United States. In 1997, the year prior to initiation of dual T4/TSH assays in place of primary T4 assays for congenital hypothyroidism, Michigan reported 2,381 (1.8%) positive screens and 69 positive diagnoses. In 2000, Michigan reported 6,401 (4.8%) positive screens and 105 positive diagnoses despite a similar number of newborns initially screened from 132,474 in 1997 to 134,022 in 2000.

A review of the infants treated from May 1, 1998 through December 31, 2002 revealed three probable reasons for the increase in incidence of both positive screens and diagnoses: (1) an increase in borderline positive tests due to the addition of the primary TSH assay, (2) a greater

number of referrals to medical management with variability in normal reference ranges by commercial laboratories for confirmatory serum retests, resulting in a greater number of positive diagnoses, and (3) treatment of infants with normal T4 values but persistent, slightly elevated TSH values.

Following this review, a meeting of stakeholders was convened to review proposed screening criteria. As a result, the Michigan Department of Community Health clarified the state objective for screening for primary congenital hypothyroidism, developed a new age-adjusted algorithm for identifying newborns with positive screens utilizing primary TSH assays and eliminating T4 assays, and recommended retests with dried blood spots rather than serum.

Implementation of TMS Instrumentation in Michigan Newborn Screening

E. Stanley and H. Hawkins, Michigan Department of Community Health, Lansing, MI

Michigan Public Health Code Act 368 of 1978 was amended on December 12, 2002 to include MCADD to the newborn screening panel effective April 1, 2003. Program and laboratory preparations had begun months earlier in anticipation of this legislation. An \$11.00 fee increase to cover the cost of the additional test was included in the amendment.

The underivatized method for MS/MS analysis of amino acids and acylcarnitines from PerkinElmer was selected. Two Wallac MS2 Tandem Mass Spectrometers were installed and validated. A pilot study was conducted with over 6,600 specimens to determine the cutoff levels to be used. Information from other screening programs was considered when establishing the assay cutoffs. The assistance from PerkinElmer in instrument setup, training, and data collection was vital to the successful initiation of this technology in our laboratory.

The MSUD and PKU assays were converted from fluorometric procedures to the MS/MS on the start date. There was significant decrease in false positive results in these disorders.

Now that the robustness of this technology with our staff has been validated and the appropriate follow-up measures are in place, the next phase of expansion is being implemented for tyrosinemia, homocystinuria, citrullinemia, and argininosuccinic aciduria.

National Coalition for PKU & Allied Disorders Metabolic Conference, June 25-26, Novi

Michigan hosted the annual National Coalition for PKU and Allied Disorders Metabolic Conference for parents, professionals, and affected individuals. Sandy LaPrad, the Newborn Screening Program parent consultant, was instrumental in planning the conference and organized a special break-out session for Michigan families with children affected by metabolic disease during the conference. Scholarships to defray the registration fee and cost of travel were advertised to more than 700 known Michigan families with newborn screening metabolic disorders. Nine families requested assistance, which was provided from the Newborn Screening

Program. Over 60 families from Michigan attended the conference. Session topics included phenylketonuria, organic acidemia, fatty oxidation disorders, homocystinuria, tyrosinemia, and newborn screening. Many national and international experts presented to over 325 conference attendees.

Internship of Medical Student through University of Michigan Summer Biomedical Research Program

The Newborn Screening epidemiologist mentored a medical student from the University of Michigan Summer Biomedical Research Program. Ms. Christina Weng spent three months assessing physician attitudes toward and experience with patient care for women of childbearing age affected by phenylketonuria through surveys to obstetricians/gynecologists and perinatologists. As a result of her findings, she developed a comprehensive PowerPoint presentation titled “One Disorder, Two Generations: Caring for the PKU Woman in her Reproductive Years” to be distributed to obstetricians/gynecologists and perinatologists throughout Michigan. An abstract of her work follows:

Physician attitudes towards and experience with patient care for women of childbearing age

Christina Weng, under the mentorship of Rebecca Malouin, Ph.D., M.P.H.
Dept. of Ob/Gyn & Mich. Dept. of Community Health, U of M Medical School, Ann Arbor, MI

Current guidelines for the treatment of phenylketonuria (PKU), a rare metabolic disorder, support a phenylalanine-restricted diet for life for affected women of childbearing age to prevent severe birth defects. We assessed physicians’ awareness of these recommendations as well as their attitudes towards treating these women with the objective of developing a physician-directed informational CD-ROM to enhance their care for this patient population.

Surveys were mailed to 44 obstetrician/gynecologists and 47 perinatologists practicing in southeastern Michigan. Physicians were asked to anonymously respond to 16 questions regarding their experience with and attitudes towards treating women of reproductive age affected by PKU.

We obtained a 58.2% response rate, with slightly more male respondents. The average physician had practiced 10 or more years, had cared for one to three expectant/childbearing-aged women with PKU, and felt neutrally about/disagreed with the statement “I am comfortable with my knowledge of the condition of PKU and the appropriate recommendations for its treatment.” Their perception of and willingness to treat patients with PKU versus those without PKU did not differ significantly. 81% agreed/strongly agreed that it was a physician’s responsibility to recommend birth control to women who were off-diet.

Although physicians may not feel completely at ease with their awareness of proper care for patients of childbearing age with PKU, they were not found to exhibit an aversion toward these

women regarding the provision of medical services. We hope that our CD-ROM, which will be distributed to obstetricians, gynecologists, and perinatologists across the state of Michigan, will prove to be a beneficial resource for the physician, promote better care for his or her patients with PKU, and ultimately generate improved medical outcomes for both mother and child.

Technical Review by National Newborn Screening And Genetics Resource Center, October 13-15

In order to accelerate progress toward conforming with the American College of Medical Genetics (ACMG) task force recommendations on a uniform newborn screening panel and system, the Newborn Screening Program requested and was granted a technical review site visit by the National Newborn Screening and Genetics Resource Center (NNSGRC). In November, 2004, a team from NNSGRC visited Michigan for several days. They conducted a thorough review of the laboratory functions and follow-up program at the Michigan Department of Community Health, and the medical management system. A written report is pending.

Participation in Regional Genetics Collaborative

Janice Bach, the state genetic coordinator, serves as project co-director for the Health Resources and Services Administration-funded Region 4 Midwest Collaborative. The collaborative includes three clusters of activities, focused on clinical diagnosis and management, newborn screening and tandem mass spectrometry, and public health infrastructure. Dr. Kevin Cavanaugh, the director of the Newborn Screening Laboratory director is participating in the tandem mass spectrometry cluster activities under the leadership of Dr. Piero Rinaldo in Minnesota. Several other newborn screening staff are participating in all seven of the public health cluster working groups addressing various aspects of public health genetic services and newborn screening follow-up. Dr. Rebecca Malouin, the newborn screening epidemiologist, leads a working group addressing improvement and integration of child data systems.

Policy on Retention and Use of Residual Dried Blood Spot Specimens

The Michigan Department of Community Health, in accordance with legislation mandating the administration of the newborn screening program, has developed policies and procedures for the retention and use of residual dried blood spots.

Upon completion of the laboratory testing for newborn screening disorders and in compliance with the legislation, the state has developed a newborn screening and dried blood spot retention schedule of 21.5 years. This schedule meets the following requirements: (1) it is consistent with nationally recognized standards of practice and federal laboratory accreditation regulations; (2) the disposal is in compliance with section 13811 of the Public Health Code; (3) the disposal is conducted in the presence of a witness; (4) that a written record of the disposal be maintained, and that the witness signs the record.

Dried blood spots may be used for forensic, diagnostic or research purposes after all required newborn screening tests have been completed. As written in the public health code, if blood specimens are to be used for medical research during the retention period, the research must be conducted in a manner that preserves the confidentiality of the test subjects and is consistent to protect human subjects from research under subpart A of part 46 of subchapter A of title 45 of the code of federal regulations.

In December 2004, the Newborn Screening Advisory Committee designated a subcommittee to review the Michigan Department of Community Health policy and procedures for retention and use of the residual dried blood spots. The subcommittee plans to meet regularly and to report recommendations to the Newborn Screening Advisory Committee in 2005.

State and National Resources

Online Course for Newborn Screening Education

The Michigan Department of Community Health Newborn Screening Program developed a free online program for newborn screening education, which continued to be popular throughout the year. The objective of the course is to help individuals better understand and carry out their role within the newborn screening program. The course contains valuable information for everyone involved in the newborn screening process including clerical staff, phlebotomy/laboratory staff, nurses, physicians, midwives, and mailroom staff.

There are nine modules in the course. Each module includes a section dedicated to common questions and answers to help reinforce material. Upon completion of the course, a quiz is available. If the viewer receives a passing score, a certificate of completion is automatically created and available for printing. The newborn screening program anticipates that hospitals will use this program as part of their mandatory competencies. Exciting features of the course include web-based accessibility and ease of use, ability for a user to complete the course in sections or in one sitting, completion time of one hour or less, and links to valuable newborn screening information and resources.

To access the course, please visit www.training.mihealth.org. Follow the directions to log in (free), select “Newborn Screening,” then begin the course. Contact Midge McCaustland, R.N.C., M.S.N., Nurse Consultant/Newborn Screening Educator, with any questions about the course by email at mccaustlandm@michigan.gov or by telephone at 517-335-8588.

State Resources

The **Michigan Newborn Screening Follow-up Program** provides follow-up activities for identified infants. Program efforts assure that: 1) all Michigan infants receive newborn screening; 2) infants with positive screening tests have access to treatment and a medical home; and 3) infants with positive screens receive long-term follow-up and monitoring of health outcomes.

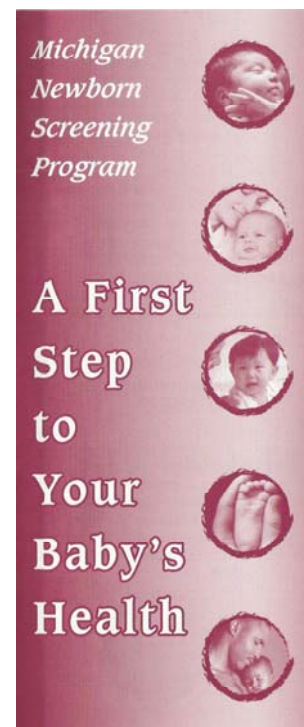
Michigan Newborn Screening Program

1-866-852-1247

NBS-Parent@michigan.gov

Michigan Newborn Screening Parent Consultant 1-866-852-1247

The **Newborn Screening Update** is a newsletter prepared quarterly for hospital staff and midwives. Please visit www.michigan.gov/newbornscreening



The **Endocrine Follow-up Program** is sponsored by the state of Michigan's Newborn Screening program and is located within the University of Michigan Department of Pediatrics, Division of Endocrinology. This follow-up program monitors all infants with screens in the state which are abnormal for the two endocrine disorders on the screening card. The Endocrine Follow-up office is notified when a baby's screen is abnormal for congenital hypothyroidism or congenital adrenal hyperplasia, two disorders which need prompt diagnosis and treatment. The goal of the follow-up office is to make sure the baby gets a repeat newborn screen or a referral for more intensive evaluation. Most abnormal screens are followed by a repeat screen, but some screens are followed by a special blood test, depending on the case.

University of Michigan Pediatric Endocrinology

734-764-5175

<http://www.med.umich.edu/1libr/tests/testn04.htm>

The **Children's Hospital of Michigan Metabolic Program** is responsible for the diagnosis and medical management of all newborns with the eight metabolic disorders detected by newborn screening. In addition to the metabolic disease clinic, the program provides biochemical and molecular genetics diagnostic laboratory services.

Children's Hospital of Michigan Metabolic Clinic

1-866-44CHMMC (442-4662)

The goal of the **Michigan PKU website** is to offer families affected by PKU helpful information and support.

Michigan PKU

www.michigan-pku-org

Local health departments provide information about **Children's Special Health Care Services (CSHCS)**. CSHCS helps to coordinate and pay for hospital and outpatient medical specialty care. Help may also be available for travel expenses related to a child's medical care. More than 2,000 diagnoses are eligible for coverage.

Children's Special Health Care Services

1-800-359-3722

Children's Special Health Care Services Family Phone Line

1-800-359-3722

Children with developmental disabilities who reside with their birth or adoptive parents and are in need of intensive community living supports and/or private duty nursing services may be eligible for the **Children's Waiver Program**. Contact your local Community Mental Health Services Program directly for more information. For a telephone number, call **(517) 374-6848**.

Early On® Michigan provides services for eligible children from birth to age three and their families regardless of income. The services may include family training (skill building), counseling (family, group or individual), home visits, psychological services, service coordination, health services, nursing services, social work services, nutritional counseling, or transportation.

Early On® Michigan

1-800-EARLY-ON (800-327-5966) voice and TDD

www.earlyonmichigan.org

The Birth Defects Follow-up Program at the Michigan Department of Community Health (MDCH) can help with referrals for support and services. The program provides resource information for families and health care providers.

1-866-852-1247

e-mail: BDRFollowup@michigan.gov

Responding to the needs of Michigan residents, **Michigan Genetics Connection** is a central source of information on genetic health care and related topics.

Michigan Genetics Connection

www.migeneticsconnection.org

National Resources

ASA Kids is a support group for those dealing with argininosuccinic aciduria. This website site allows ASA families to communicate with each other about issues related to living with ASA.

ASA Kids

www.asakids.org

The **Biotinidase Deficiency Family Support Group** website is devoted to supporting those affected by biotinidase deficiency. The support group is a non-profit volunteer organization. The mission is to establish a forum to exchange information about biotinidase deficiency among affected individuals and with medical professionals and to advocate for the inclusion of biotinidase testing in all newborn screening programs.

Biotinidase Family Support Group

<http://www.biotinidasedeficiency.20m.com/>

The Texas Newborn Screening Case Management Program website offers two publications, “**Congenital Adrenal Hyperplasia: Handbook for Parents**” and “**The ABC’s of Congenital Adrenal Hyperplasia**”.

www.tdh.state.tx.us/newborn/hand_cah.htm

The MAGIC Foundation is a national nonprofit organization providing support services for the families of children afflicted with a wide variety of chronic and/or critical disorders, syndromes and diseases that affect a child's growth. Some of the diagnoses are quite common while others are very rare.

The MAGIC Foundation

<http://www.magicfoundation.org/divisions/thyroiddisorders.htm#general>

The **FOD Communication Network** is intended to be used as a resource for families, friends, doctors, researchers and others who would like to support, educate and provide a forum for the sharing of ideas and concerns for those whose lives have been touched by a fatty oxidation disorder.

FOD Family Support Group

336-547-8682

www.fodsupport.org

Galactosemic Families of Minnesota is an organization developed by a group of families from Minnesota and surrounding states living with galactosemia. The group was founded in 1998, for

the purpose of sharing information about the disorder and to get families in touch with each other for support and education.

Galactosemic Families of Minnesota
www.galactosemia-mn.com

Parents of Galactosemic Children, Inc. (PGC) is a national, non-profit, volunteer organization whose mission is to provide information, support, and networking opportunities to families affected by galactosemia.

Parents of Galactosemia Children Inc.
www.galactosemia.org

The **MSUD Family Support Group** is a non-profit 501 (c)(3) organization for those with MSUD and their families and includes healthcare professionals and others interested in MSUD.

MSUD Family Support
www.msud-support.org

Children's PKU Network (CPN) was founded in 1991 to address the special needs and concerns of individuals with phenylketonuria (PKU) and their families. CPN is a non-profit organization dedicated to maintaining an agenda of public awareness, education, and direct assistance through a variety of programs, to help people with PKU and other metabolic disorders reach their full potential.

Children's PKU Network
www.phunetwork.org

The **National Coalition for PKU and Allied Disorders** is a nonprofit organization comprised of individuals, metabolic support groups and professionals directly involved with issues related to errors of metabolism requiring low protein diet including PKU, MSUD, HCU, the AO's, UCD's and tyrosinemia.

National Coalition for PKU and Allied Disorders
1-877-996-2723
www.pku-allieddisorders.org

The **National Urea Cycle Disorders Foundation** is a non-profit organization dedicated to the identification, treatment and cure of urea cycle disorders. The organization was formed in 1988 by parents whose children were affected to provide a primary resource for information and education, and to support and stimulate research on urea cycle disorders. The foundation is operated and supported by the volunteer efforts of families with children suffering from UCDs. The organization is a supportive network of families, friends, and medical professionals.

National Urea Cycle Disorders Foundation
800-386-8233
www.nucdf.org

The American Sickle Cell Anemia Association (ASCDAA) is an organization that provides quality and comprehensive services through diagnostic testing, evaluation, counseling and supportive services to individuals and families at-risk for sickle cell disease. The American Sickle Cell Association is a private nonprofit 501(c)3 organization in Cleveland, Ohio. The ASCDAA was founded in 1971 and is the oldest sickle cell research, education, and social services organization in the United States.

American Sickle Cell Anemia Association
216-229-8600
<http://www.aSCDAA.org/>

About Sickle Cell Disease is a website dedicated to educating the public about the structure of sickle cell hemoglobin and the mechanism of sickle cell disease.

About Sickle Cell Disease
www.sicklecellinfo.net

The mission of the **Sickle Cell Disease Association of America, Inc.** is to promote finding a universal cure for sickle cell disease while improving the quality of life for individuals and families where sickle cell related conditions exists.

Sickle Cell Disease Association of America, Inc.
1-800-421-8453
www.sicklecelldisease.org

The **National Newborn Screening and Genetics Resource Center (NNSGRC)** provides information and resources in the area of newborn screening and genetics to benefit health professionals, the public health community, consumers and government officials.

National Newborn Screening and Genetics Resource Center (NNSGRC)
<http://genes-r-us.uthscsa.edu/>

The **Family Village**, supported by the Waisman Center, University of Wisconsin-Madison, is a global community that integrates information, resources, and communication opportunities on the Internet for persons with cognitive and other disabilities, for their families, and for those that provide them services and support. The community includes informational resources on specific diagnoses, communication connections, adaptive products and technology, adaptive recreational activities, education, worship, health issues, disability-related media and literature, and much, much more.

Family Village
www.familyvillage.wisc.edu

Gene Reviews is funded by the National Institutes of Health and provides current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling. GeneTests promotes the appropriate use of genetic services in patient care and personal decision-making.

Gene Reviews
www.genetests.org

The mission of **the March of Dimes Birth Defects Foundation** is to improve the health of babies by preventing birth defects and infant mortality.

March of Dimes
www.marchofdimes.com

Acknowledgements

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Pediatric Endocrinology Advisory Committee

The Michigan Department of Community Health would like to thank members of the Pediatric Endocrinology Advisory Committee for their time and expertise. Members of this committee meet quarterly with Newborn Screening Program staff and the Endocrine Follow-up Program at the University of Michigan to advise the program on screening for and medical management of endocrine disorders.

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